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Letter to the Editor

Silibinin chirality

Dear Editor,

I am writing you in respect of the paper "Tushar Kanti Maiti, Kalyan Sundar Ghosh, Anirban Samanta, Swagata Dasgupta: The interaction of silibinin with human serum albumin: a spectroscopic investigation. *Journal of Photochemistry and Photobiology A: Chemistry* 194 (2008) 297–307.

Authors published spectroscopic (UV–vis, FT-IR and CD) analysis of silibinin binding to HSA. I am sorry to say that authors proved complete ignorance of the stereochemistry and diastereomeric composition of natural silibinin they used for their study.

Natural silibinin is an approximate equimolar mixture of two diastereomers silibinin A, (2*R*,3*R*)-2-[(2*R*,3*R*)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one and silibinin B (2*R*,3*R*)-2-[(2*S*,3*S*)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one. Absolute configuration of both silibinin A and B was determined [1,2]. Optical rotation ($[\alpha]_D^t$) is the easiest method to assign the absolute configuration of both compounds: natural silibinin (mixture of A and B in the rate ca 1:1 – usually B is slightly prevalent) has $[\alpha]_D^{23} = 11.4$ ($c = 0.29$, acetone) [3], silibinin A has $[\alpha]_D^{23}$ higher than the mixture +20 ($c = 0.21$, acetone) and silibinin B has $[\alpha]_D^{23}$ lower −1.07 ($c = 0.21$, acetone) [1]. It should be noted that CD spectra of both diastereomers differ substantially.

In the paper authors give the name of silibinin (p. 1, Introduction par. 1) that is actually "silibinin B" but in the Fig. 1 A structure of silibinin B is given (however with wrong description of chirality at C1 (*R*) and C3 (*R*)). Also the description of Fig. 1. A is incorrect (chirality at C1 (*R*) and C3 (*R*)). In the Materials author give Sigma as a source of silibinin used in this study. This silibinin is a "natural" silibinin isolated by extraction and it is a mixture of both silibinin A and B. Generally, if silibinin is mentioned in the literature without any specific description it is considered to be a mixture of A and B. Unfortunately, literature is full of mistakes - even Merck Index 14th Ed. gives a structure of silibinin a the single compound (silibinin A) ignoring the above facts. Detailed analysis of this problem is given in two papers "V. Šimánek, V. Křen, J. Ulrichová, J. Vičar, L. Cvak: Silybin... - what is in the name?" Hepatology 32 (2000) 442–443" [4] and quite recently D. J. Kroll, H. S. Shaw, N. H. Oberlies: Milk Thistle Nomenclature: Why It Matters in Cancer Research and Pharmacokinetic Studies. Integr Cancer Ther 2007; 6; 110 [5].

Now the authors of this paper obviously used a mixture of two diastereomers for their "wet" experiments but for the docking only a structure of a single diastereomer "A" has been used (Fig. 2). Then, naturally, distances in the Tab. 2, namely those to Trp214 and Asp451 are valid only for this respective diastereomer. This is very important as on these data most of discussion of the binding experiments is based (red shift of fluorescence spectra etc.). In fact, when working with silibinin AB, the authors had in their experiments half concentration of the compound A (concentration!) but also half of concentration of another diastereomer, which could distort chiroptical measurement. Measurement of circular dichroism (Fig. 8) is also erroneous from the above reasons.

The major flaw of this paper, which obviously misled the referees of this paper and also its readers is the fact that authors describe silibinin here as an optical pure entity, whereas they had in hands a mixture. Authors were notified about this fact in their previous submission to BBA- Proteins and Proteomics (where I served as a referee and in my report I have depicted all the above problems). Despite this fact authors are now publishing the same (partly) incorrect data.

Therefore, I am proposing that the paper is retracted or at least part of it; or appropriate erratum is published explaining that the compound used in this study was not pure contrary to the single diastereomer used in the docking and all errors in nomenclature of silibinin and figures in the respective paper are corrected.

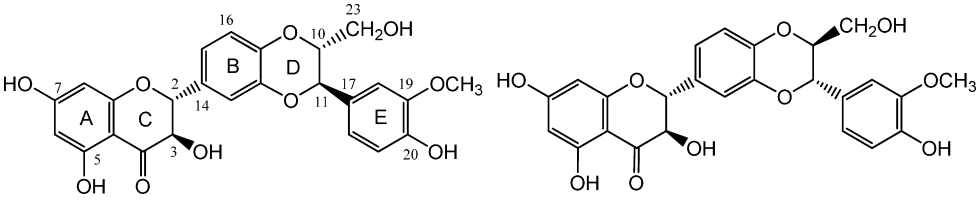

Fig. 1. Structures and chirality of silibinin diastereomers.

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